ASSESSING HUMAN EPIDEMIOLOGIC DATA ON DIET AS AN ETIOLOGIC FACTOR IN CANCER DEVELOPMENT*

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The epidemiology of cancer among human populations is an observational, not an experimental science. The closest that an epidemiologist comes to experimental data is a randomized controlled trial, very difficult to conduct because of practical and ethical considerations. Consequently, epidemiologists are limited primarily to interpreting naturally occurring phenomena. Before specifically examining the relationship between diet and cancer, it is useful to recall the five criteria used in 1964 by the Surgeon General's Advisory Committee on Smoking and Health in establishing a "causal" association between cigarette smoking and lung cancer.[1] The first is consistency, which implies that diverse methods of approach, such as retrospective and prospective studies, lead to the same conclusion. The second is strength, which measures the relative risk and can yield a judgment on the size of the effect of an etiologic factor and whether this factor is important in producing the disease. Third is specificity, which implies the precision with which a factor predicts the occurrence of a disease in a given individual. Fourth is temporal relationship, which means that exposure to a causal agent must precede in time the onset of the disease it produces. Fifth is coherence, which means that all major data are compatible with a genuine association. It is possible to conclude that cigarette smoking "causes" lung cancer because these five criteria are supported by such a vast amount of data, especially the fact that the lung cancer rate is so much higher in cigarette smokers than in nonsmokers.

However, this conclusion is not yet possible with the existing data relating diet and cancer in spite of the fact that some investigators believe

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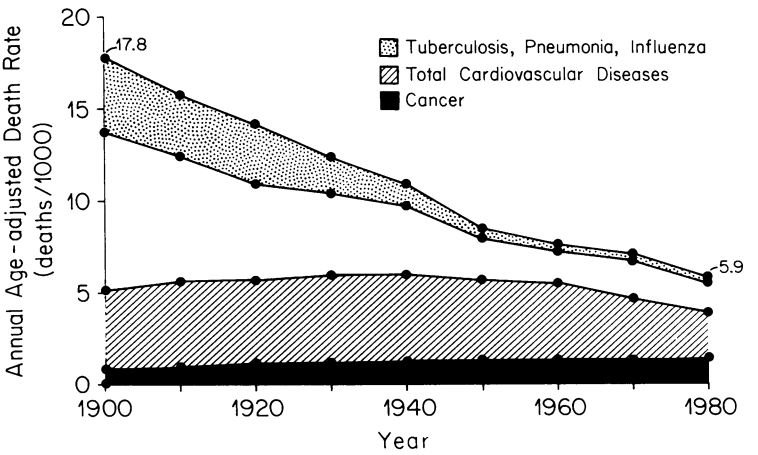

Fig. 1. Annual age-adjusted death rate for U.S. population by major cause every 10 years, 1900-1980, standardized to the 1940 U.S. population.

as much as 40% of male cancer and 60% of female cancer is related to diet.[2,3] Any given dietary theory is advocated by citing evidence that supports the theory and ignoring contradictory evidence.

I would like to begin my assessment by examining what I think are the two most obvious facts about cancer that one must face. First is the strong exponential relationship between the cancer death rate and aging.[4,5] During a one-year period, about 0.2% of all people will die of cancer, but this varies from 0.01% for people under age 25 to about 2% for people above age 85—a 200-fold difference. So, in practical terms, cancer is primarily a disease associated with aging. Second is the relative constancy of the age-adjusted cancer death rate since the beginning of the century.[4,5] Although the age-adjusted total death rate has continuously declined throughout this century, from about 17.8 deaths/1,000 in 1900 to about 5.9 per 1,000 in 1980, including declines in essentially all the major diseases, the overall cancer rate has remained almost constant at around 1 death/1,000,[4,5] as seen in Figure 1. However, the nature of the cancer problem has changed in the sense that stomach cancer has declined from about 40% to about 3% of all cancer deaths and lung cancer has risen from essentially 0% to 25% of cancer deaths. Excluding lung cancer, the remaining cancer rate has moderately declined during recent decades. Further, the cancer rate has been declining gradually in people under age 45 and only three out of eight cancer deaths now occur in people under age 65.

Probably the best established relationship involving diet and cancer is between alcohol consumption and upper alimentary tract cancer in most Western countries.[6] However, the primary dietary factors of current interest are fat, fiber, vegetables, and vitamins. The primary "diet-related" cancers are generally considered to be stomach, colorectal, and breast cancer.[2,3]

Retrospective case-control studies date back to those of Percy Stocks[7] and Frederick Hoffman[8] during the 1930s. Since then there have been at least 20 major case-control studies and three prospective cohort studies, primarily focused on diet and cancer.[6,9] These studies have taken place in England, Finland, Israel, Norway, Canada, Japan, Hawaii, and several areas within the continental United States. Several individual dietary items have been implicated with a risk factor of the order of 2 to 3. For instance, high consumption of meat, beef, fat, and beer, low consumption of fiber, various groups of vegetables, and dietary vitamins A and C, and low serum levels of vitamin A and cholesterol have all been associated with increased cancer risk in one or another of these studies. But, integrating the studies yields substantial conflicting findings: beef consumption was associated with colon cancer in Hawaiian Japanese,[10] but not in three groups of native Japanese.[11,12] Probably the most consistent finding is the association observed for the past several years between low levels of vitamin A (generally below the recommended dietary allowance) and increased risk of cancer, particularly lung cancer.[13] This relationship is somewhat unexpected because lung cancer is already so strongly linked with cigarette smoking. In any case, no dietary factor yet satisfies the five criteria for causality.

Because the retrospective and prospective studies have been inconsistent and inconclusive, the "strongest" available epidemiologic data relating diet to cancer are international geographical correlations between, for instance, per capita fat consumption and age-adjusted colon and breast cancer rates.[14,15] But there are many weaknesses in these correlations. For example, fat consumption for each country is usually estimated from the national sales and disappearance of food stuffs but often does not agree with fat consumption obtained from direct dietary surveys such as the 1971-1974 U.S. Health and Nutrition Examination Survey conducted by the National Center for Health Statistics.[16] Note that the data in often cited Figures 2 and 3 are not consistent in fat-consumption levels. Figure 2 shows that American men consume 55 grams per day,[14] whereas the Survey indicates 100 grams per day.[16] Figure 3 shows that American women

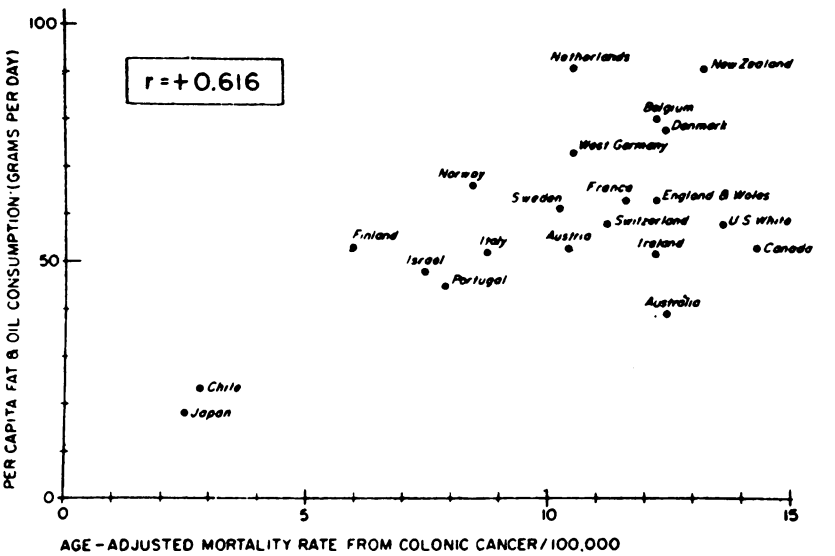

Fig. 2. Large-bowel cancer mortality (1966 to 1967) and dietary fat and oil consumption (1964 to 1966) in males. Reproduced by permission from Wynder, E. L.: The epidemiology of large bowel cancer. *Cancer Res. 35*:3389, 1975.

consume 150 grams per day,[15] whereas the survey indicates 67 grams per day.[16] Further, correlations between cancer rates and fat intake in 64 areas within the United States, based on survey data, are essentially zero[17] as shown in Figure 4; this is far different from the strong international correlations. In other words, there is a large variation in colon cancer rates with essentially constant fat intake throughout the United States.

Another form of epidemiologic evidence involves migrant studies. Japanese who migrate from Japan to the United States have increased rates for colon and breast cancer relative to rates in Japan.[18,19] These increased rates are frequently attributed to the substantially increased fat intake of Japanese migrants relative to native Japanese.[2,3] However, this is selective use of data. In spite of increases in colon and breast cancer, the total cancer rate among Japanese-Americans remains essentially unchanged and their total death rate decreases and remains lower than that of native Japanese.[18,20] American-born Japanese are especially healthy. Based on survey data, American Japanese appear to have almost the same dietary fat intake as American whites, about 80 grams per day—comprising about 40% of total caloric intake[16]—and yet their overall death rates remain relatively low. In summary, the 1970 standardized mortality ratio

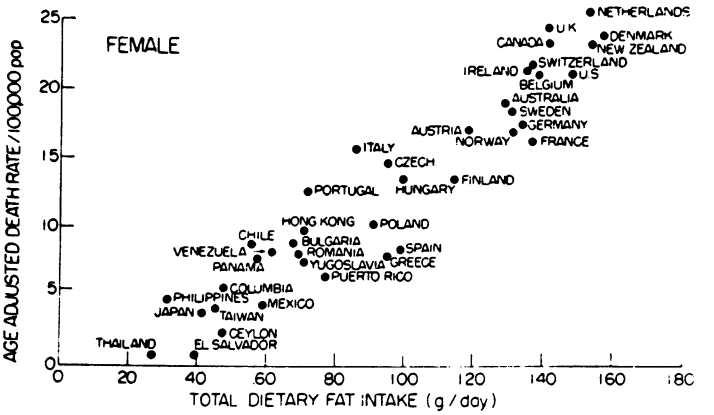

Fig. 3. Correlation between per capita consumption of dietary fat and age-adjusted mortality from breast cancer in different countries. The values for dietary fat are averages for 1964 to 1966 and those for cancer mortality are for 1964 to 1965, except in a few cases where data were available only for 1960 to 1961 or 1962 to 1963. Reproduced by permission from Carroll, K. K.: Experimental evidence of dietary factors and hormone-dependent cancers. *Cancer Res. 35*:3379, 1975.

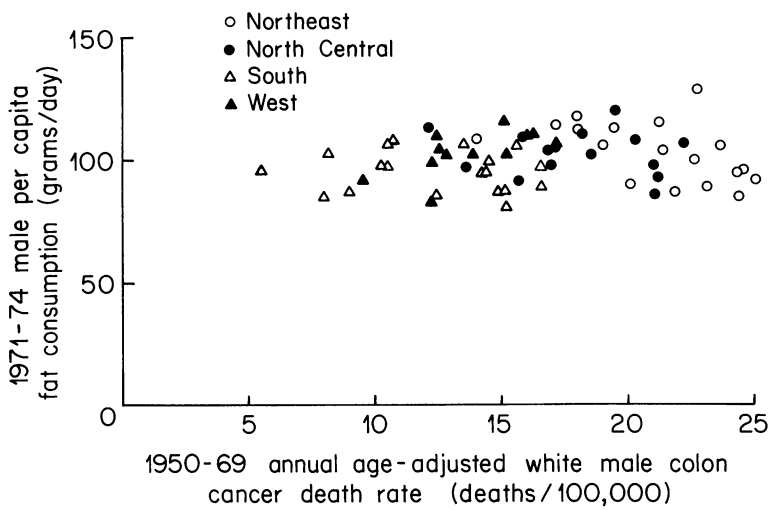

Fig. 4. Mortality and fat consumption in males in 64 areas within the U.S.

for Japanese-Americans compared with American whites is about 50% for all causes, 80% for total cancer, 75% for colon cancer, and 30% for breast cancer (see table).[19,20] These and other data indicate that Japanese are the healthiest race in America in spite of an "Americanized" diet.[20]

In addition to Japanese-Americans, at least two American white sub-

1968-72 STANDARDIZED MORTALITY RATIOS RELATIVE TO 1970 U.S. WHITES[19,20]

Cause of death	*Japanese*		*Japanese Americans*						*U.S. Whites*	
			Total		*Issei (Japanese born)*		*Nisei (American born)*			
	Males	*Females*	*Males*	*Females*	*Males*	*Females*	*Males*	*Females*	*Males*	*Females*
Breast cancer	—	20	—	31	—	15	—	40	100	100
Colon cancer	31	32	75	79	67	84	84	72	100	100
Rectum cancer	115	136	113	87	120	86	105	89	100	100
Colorectal cancer	53	51	85	80	80	84	90	75	100	100
Stomach cancer	846	882	351	408	409	410	287	404	100	100
Total cancer	93	87	84	73	105	87	66	61	100	100
All causes	~90	~100	~50	~50					100	100

populations have relatively low "diet-related" cancer rates without any obvious relationship to diet. Mormons, for instance, advocate abstention from tobacco, alcohol, and caffeine-containing beverages, as well as dietary moderation. The average standardized mortality ratio for active Mormons in California and Utah is about 60% for total cancer, 65% for colon cancer, and 80% for breast cancer.[21] Mexican-Americans, defined as American whites born in Mexico, have a standardized mortality ratio of about 95% for total cancer, only 45% for colon cancer, and 60% for breast cancer.[22] The diets of Mormons and Mexican-Americans need to be studied in much greater detail, but, based on the data now available, including the Health and Nutrition Examination Survey and the U.S. Department of Agriculture Nationwide Food Consumption Survey, they do not appear to differ noticeably from other white Americans with respect to fat consumption or other major dietary variables including intake of total calories, protein, carbohydrates, calcium, iron, magnesium, and vitamin intake from foods.[21,23] Other dietary variables such as intake of total fiber and vitamin and mineral supplements are not yet quantified.

Another way of looking at this is to compare Mormons to Seventh-Day Adventists, who abstain from tobacco, alcohol, and caffeine, and, in addition, eat very little meat. Mormons and Adventists have essentially identical cancer rates, which are both about 60% of the American white rate.[21,23] These rates are also similar to those of specially selected cohorts of health conscious nonsmokers such as those in the American Cancer Society Cancer Prevention Study.[24] From this comparison, the Adventist diet per se appears to confer no lower risk of cancer among already low risk cohorts. However, this may not be as good a test as one thinks because, in spite of the low meat intake of Adventists, their total fat intake is not much lower than 40% of total calories.[23]

The rigorous way to assess the effect of a so-called "prudent" diet on subsequent cancer occurrence is to conduct randomized controlled trials on human subjects. Such trials have already been conducted for cholesterol-lowering diets and show no significant change in either cancer or total mortality rates.[25,26] Trials involving fat-lowering diets remain to be done in order properly to evaluate the low fat hypothesis.

In lieu of these dietary trials, probably the best epidemiologic evidence that can be hoped for is that an unusually low rate of cancer can be demonstrated in a group which adopts and maintains a diet different from the typical American diet. In an effort to find an optimum diet, as many variations as possible should be explored. For instance, it would be very

valuable to locate people on long-term, low fat, high fiber, high vegetable, and/or high vitamin diets and examine their cancer rates. It may be difficult to locate many genuine vegetarians because the Health and Nutrition Examination Survey showed that only 0.1% of Americans never use meat, poultry, or fish.[16] But people with unusual diets can be found. In this spirit, I am currently examining a group of very health-conscious persons who use supplements of vitamins and minerals far in excess of the recommended dietary allowance. So far, I do not yet have enough data to show any specific relationship between their diet and cancer rate, but the group is worth further study.

In summary, epidemiologic studies as a whole have not yet uncovered any "causal" relationship between diet and cancer and have not yet demonstrated any specific diet which in and of itself leads to a greatly reduced cancer death rate. Further, it appears there are substantially lower than average cancer rates among several groups of nonsmokers with a fairly average American diet. However, a number of interesting leads should be vigorously pursued with the goal of precisely determining an optimum diet. Properly understanding the dramatic decline in stomach cancer deaths would be a great accomplishment for cancer prevention. Before people get their hopes up that a new diet will prevent cancer, it should first be demonstrated that lung cancer can be prevented by smoking cessation. In the meantime, Americans can take some comfort in the fact that, even though their diet may not be optimal, they are currently experiencing the lowest total death rate and highest life expectancy in American history.[5]

Questions and Answers

QUESTION: Please explain Figures 2 and 3. The data seem misleading.

DR. ENSTROM: I presented Figures 2 and 3 as examples. These two published figures demonstrate the difficulties in using gross food-consumption data from various countries rather indiscriminantly. For example, such data indicate that the cancer rates in countries such as Thailand and El Salvador are almost zero, but I don't believe that the true cancer death rates in those countries are that low. What generally happens in such countries is that the disease is not reported on death certificates.

QUESTION: What is the source of your data on comparative death rates?

DR. ENSTROM: The comparison of death rates from 1900 to 1980 is

based on available data published by the National Center for Health Statistics. In 1900 only 40% of the country's population was in the death-registration area, which included mainly such eastern states as Massachusetts and New York. Cancer was probably underreported in those early days. Some of the increase during the early decades of the century was probably due to increased reporting of cancer deaths and this would make the total cancer death rate curve even flatter.

Since 1940 the diagnostic methods and the coverage over the entire United States have been consistent and there has only been about a 10% increase in the entire cancer death rate. This indicates that, relatively speaking, there have been vast changes in mortality from certain other diseases but not from cancer.

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